

Combining Microarrays With Comparative Genomics To Elucidate Gene Regulatory Networks For Normal and Perturbed Forebrain Development

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INTRODUCTION: Perturbation to forebrain development is linked to the toxicity of numerous environmental agents as well as in the etiology of several neurodevelopmental disorders.



Disorders:

- Schizophrenia (LaMantia et al. 1999)
- Autism (Perry et al. 2001)
- ADHD (Kamimura et al. 2001)

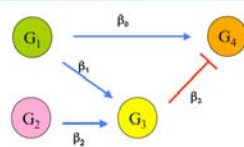
Environmental Agents:

- Ethanol (Miller et al. 1995)
- Retinoic Acid (Clark et al. 2004)
- Dioxin (Henshel et al. 1997)
- Methylmercury (Choi et al. 1986)
- Organophosphate pesticides (Slotkin et al. 1998)

METHODS: Computational and Bioinformatics Tools for Discovery and Quantitation of Gene Networks.

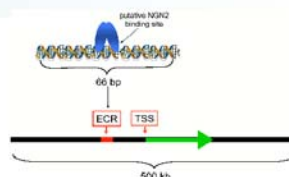
Bayesian Network Analysis:

- Identification of the optimal gene network given a gene expression dataset (Yamanaka et al. 2004 EHP 112(16): 1614-1621).
- Quantification of the strength of each linkage in a gene network given a gene expression dataset (Toyoshiba et al. 2004 EHP 112(12): 1217-1224).

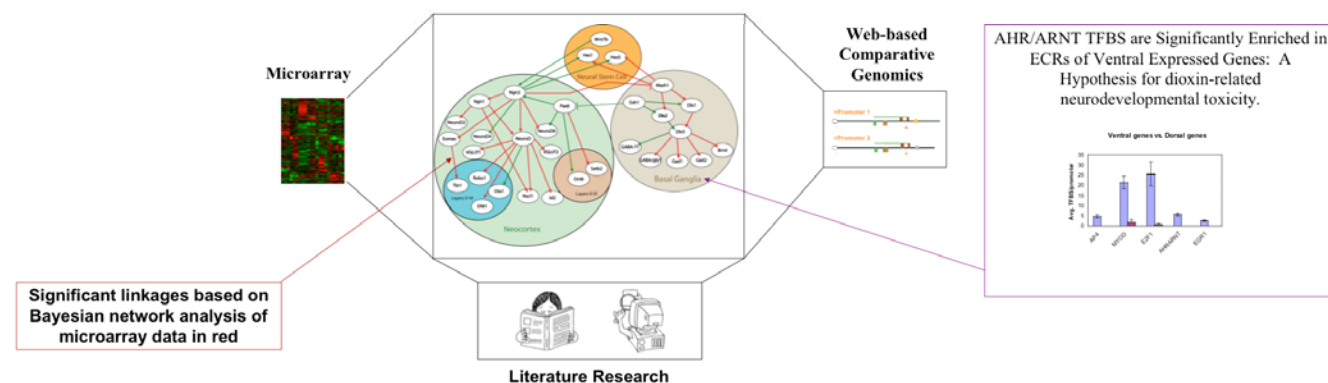


Comparative Genomics:

- Whole genome alignments (human, mouse, chicken, frog, and pufferfish)
- Submit evolutionarily conserved regions (ECRs) to transcription factor binding sites (tfbs) search algorithm to identify evolutionarily conserved tfbs.



RESULTS: A Gene Regulatory Network Based on Microarray Data, Literature Mining, and Comparative Genomic TFBS Analysis.



CONCLUSIONS: Computational Tools Allow for Data Synthesis and Hypothesis Generation.

- Provides a biologically-based and quantitative construct in which to evaluate cellular and molecular level forebrain developmental neurotoxicity.
- Provides a construct for comparison across species, across mechanisms, and across toxicity testing models.
- Provides a construct for current literature synthesis to prioritize future research to fill very specific data gaps.
- Provides a natural structure for linking *in vitro* and *in vivo* data to reduce, refine and replace animals in toxicology.